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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,559	11/30/2004	Eric David Moher	X-14978M	7051

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/02/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/02/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,559	MOHER ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-74* is/are pending in the application.

4a) Of the above claim(s) *47,48,54-58 and 60-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-46,49-51 and 64-74* is/are rejected.

7)☒ Claim(s) *52,53,59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Amendment dated March 1, 2007 is acknowledged with traverse. Group I is elected with claims 38-46, 49-53, and 74. Example 41 is the elected species. Upon the execution of a search, claims 59 and 64-73 were rejoined with the elected claims. Therefore, claims 38-46, 49-53, 59, and 64-74 are being examined in the current office action.

Applicants contend that it is improper for the Office to refuse to examine that which Applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. However examiner finds this argument unpersuasive because this applies to U.S. practice rather than lack of unity practice under PCT rules. Applicants next contend that unity of invention was not questioned in the international phase before the PCT preliminary examining authority. However, this argument is also not persuasive because the USPTO makes its own determination independent of what the international office determined for the parent PCT. Applicants also contend that the single general inventive concept is formula I, and all of the claims should be prosecuted together in the instant application. When the claims have unity of invention, a single product, a process of making, and a process of using, are examined together. In the instant case, the claims do not have unity of invention, and therefore, these claims are not examined together. Applicants also contend the prior art of Massey et al. (US 5,688,826) is only being used a vehicle to ensure restriction is proper. However, the technical feature that links all of the claims is a compound of formula I or II. Massey teaches formula II, and therefore, it formula II does not represent a contribution over the prior art. The restriction is deemed proper and MADE FINAL.

Information Disclosure Statement

2. The information disclosure statement filed November 30, 2004 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. Since several of the documents were foreign WIPO applications, they were considered by the abstract only.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 38-46, 50, and 74 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al. (WO 03/084610, filed 21 March 2003, claims benefit to claims benefit to two U.S. provisional cases, both filed April 3, 2002, published 16 October 2003). Johnson et al. teach compound LY 404039, which is shown below. This structure anticipates formula I of claim 38, because variable p equals 1 in the structure and variable Q equals alanyl. In the structure variables R^{10} and R^{11} are both hydrogen.

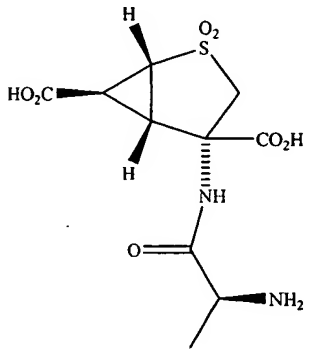

Figure 1: LY 404039

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 49-51 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al. (WO 03/084610, filed 21 March 2003, published 16 October 2003).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Johnson et al. teach the use of LY 404039 in a composition. Although it is not directly implied, the compound was synthesized in the same paper. This paper also teaches the formation of salts with amines such as

LY 404039 on page 11, lines 9-29 of the specification. Since LY 404039 has a free amine group on the alanyl group, this amine can form an acid addition salt at room temperatures. The specification states (lines 11-18): "Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, ...and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, and the like." Claims 50-51 are unobvious variants over Johnson et al. because p-toluenesulfonic acid forms a tosylate salt with a corresponding free amine and methanesulfonic acid forms a mesyl salt with a corresponding free amine. Claim 50 is also unobvious over Johnson et al. because they mention hydrochloric acid, which will form a hydrochloride salt with a corresponding free amine. Lastly, the broad claim claim 49 is unobvious because one of the possibilities for the salt is "an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion;". The motivation behind producing an acid addition salt lies in the fact that an amine is more easily handled at room temperature than when the compound is in oil form and not a salt. As is stated previously, salts are solids at room temperature.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 38-46 and 64-74 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for examples 1-13 and 41-43, does not reasonably provide enablement for compounds not encompassed by the election of group I and the species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. The factors are: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of

ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quality of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: Claims 38-46, 59 and 74, as they are currently written, encompass many compounds. In the process of doing an analysis of the possible number of compounds that *could be* encompassed by formula I, variable R^{10} can be 2 possible groups, R^{11} can be up to 3 possible groups, and X can be at least 5 groups when taking into consideration variables R^3 and R^4. The variable that encompasses the most compounds is variable A. Variable A is defined as H-$(Q)_p$-, where p is an integer from 1 to 10. Variable Q is a group taken from amino acyl. As defined in the specification on page 13, lines 24 to page 14, line 27, the "term amino acyl means an amino acyl derived from an amino acid selected from the group consisting of natural and unnatural amino acid as defined herein....". From this meaning of variable A, many compounds are encompassed by formula due to the variability of p from 1 to 10 and even more so for variable Q. Since variable Q can be an unnatural or natural amino acid, each position in variable A can be at least 20 possibilities, if one considers the twenty essential amino acids. If one considers unnatural amino acids, the possible chains encompassed by variable A explode. More unnatural amino acids are being discovered/synthesized all of the time. Therefore, the scope that is covered by formula I in claim 38 is much too broad for what is encompassed by the elected group.

The level of predictability in the art: Claims 64-73 cannot be enabled because there is no support in the specification that they may actually have the function that is claimed in these claims. The specification describes assays on pages 160-161 that *may* be used to evaluate comparative data for the compounds. The descriptions that follow only describe assays that could be applicable to the compounds that are prepared in the specification. Monn et al. (*Journal of Medicinal Chemistry*, **2007**, *50*, 233-240) have shown that different oxidized forms of bicyclic amino acids have different activity against mGlu2 and mGlu3 receptors. Tested compounds are shown in figure 1, shown below.

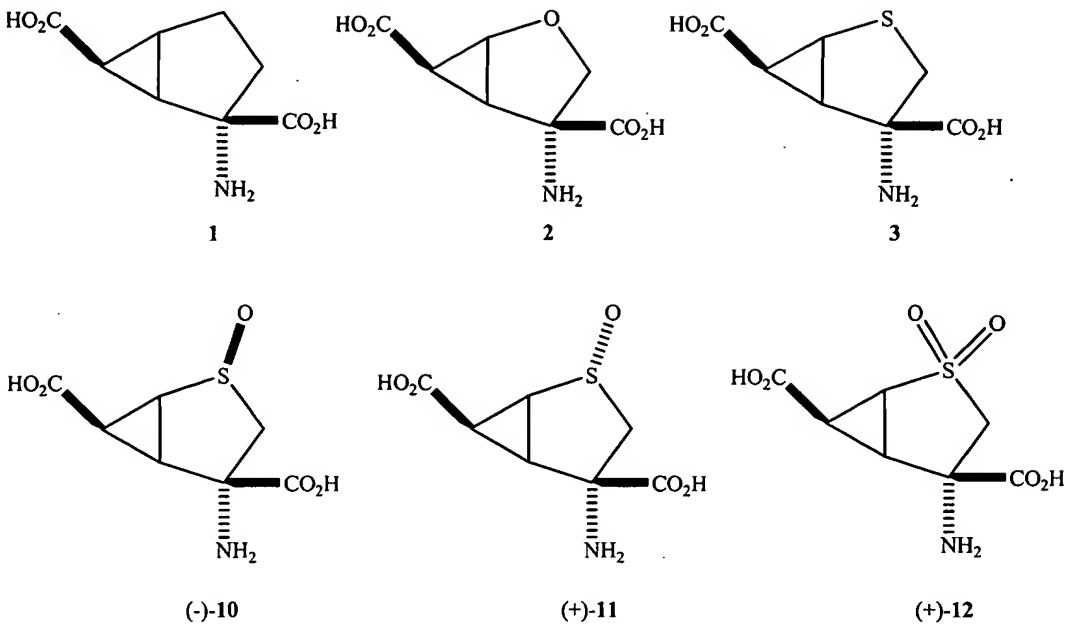

Figure 1: Prepared and/or Tested Compounds from Monn et al. (Taken from Scheme 1)

Table 1 (page 234) shows the different activities of the different forms of the compounds against mGlu2 and mGlu3 receptors *in vitro*. The introduction states (page 233): MGlu receptors are highly heterogenous with respect to their structure, function, and localization within the CNS and represent promising targets for therapeutic intervention in a multiplicity of CNS disorders." The authors measured the displacement of ^{3}H-341495 binding to membranes expressing recombinant mGlu2, mGlu3, or mGlu8, and functional (cAMP) responses in mGlu receptor expressing cells. In the displacement test, compound 1 had a displacement effect of 74.9 plus/minus 9.1 nM for mGlu2 and compound 2 had a displacement effect of 14.1 plus/minus 1.4 nM, and compound 3 had a displacement effect of 40.6 plus/minus 3.7 nM. From this data it is evident that when one ring atom changes the ring core, the activity varies. When compounds 10 through 12 were tested for the same effect, the activities once again varied wildly. Compound 10 had an activity of 508 plus/minus 9, 11 4.4 plus/minus 0.5, and 12 149 plus/minus 11. Just looking at the displacement effect for the tested compounds against the mGlu2 receptor, there is no predictability. When the stereochemistry of the S-oxidized is changed, so does the displacement. One can conclude that if the activity varies wildly based on the compound or a certain form of a compound used, different results will be obtained. The introduction also states that "Compounds **1** and **2** have been extensively studied both *in vitro* and *iv vivo*, providing important target validation data supporting hypotheses that mGlu2/3 receptors are novel targets for

the treatment...". However, authors do not state that compound 3, which is the closest of compounds 1-3 to the elected group has not been tested like compounds 1 and 2. There is no predictability for all of the compounds encompassed by formula in claims 38-39.

Due to the breadth of formula I and the lack of predictability in the art, not all of the compounds encompassed by formula I are enabled and none of the compounds are enabled for the methods of use as cited in claims 64-73 due to lack of testing shown.

Allowable Subject Matter

10. Claims 52, 53, and 59 depend on a rejected claim and would be allowable if rewritten as independent claims. They depend on rejected claim 38. In addition, examples 1-13 and 41-43 are allowable subject matter. These compounds are allowable because the closest prior art is WO 03/084610, which has already been discussed. The only other art that contains the claimed compounds and the process of preparation as described in claim 59 is from Moher et al. (WO 03/104217, published 18 December 2003), which is the PCT of this national stage application.

Applicants should amend the claims to read on elected subject matter only. As it currently stands, formula I encompasses many compounds that are not prepared in the specification. Variable A in formula can encompass many compounds because it is composed of natural or unnatural amino acids, and the peptide side chain can be a monopeptide or as big as a decapeptide.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on Monday-Friday from 7:30 to 5:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more

information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NJ

CECILIA TSANG
SUPERVISORY PATENT EXAMINER